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(71) Applicant (for all designated States except US): CEDONA PHARMACEUTICALS B.V. [NL/NL]; Oudeweg 147, NL-2031 CC Haarlem (NL).

(72) Inventors; and
(75) Inventors/Applicants (for US only) : STERK, Geert, Jan [NL/NL]; Vossegatselaan 15, NL-3583 RN Utrecht (NL). TIMMERMAN, Henk [NL/NL]; De S. Lohmanplantsoen 3, NL-2253 VM Voorschoten (NL). VAN DER GOOT, Henk [NL/NL]; Grote Belt 193, NL-2133 GW Hoofddorp (NL).

(74) Agent: KOOY, L., W.; Octrooibureau Vriesendorp & Gaade, P.O. Box 266, NL-2501 AW The Hague (NL).

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(54) Title: N-(2-SUBSTITUTED ALKYL)-N'-[(IMIDAZOLE-4-YL)ALKYL]GUANIDINE

N
|
Y_1 (II)

(57) Abstract

N-(2-substituted alkyl)-N'-[(imidazole-4-yl)alkyl]guanidines having formula (1), wherein m is 1, 2 or 3; n is 2 or 3; X is a) S, O or CH_2, and Y is a R substituted diphenylmethyl group or (10,11-dihydro)5H-dibenzo-[a-d]-cycloheptene-5-yl group, or is b) formula (II), wherein Y_1 is a R-substituted phenyl group and Y is also a R-substituted phenyl group in that Y and Y_1 need not be substituted simultaneously or Y is a R-substituted benzyl group, or is c) =CH-, and Y is a R-substituted diphenylmethylidenyl group or (10,11-dihydro)-5H-dibenzo-[a,d]-cycloheptene-5-ylidene group, R is H, alkyl, alkoxy halogen and/or trihalogen methyl, with the understanding that from all the appropriate phenyl rings one or more may be substituted by a R-substituted heterocyclic aromatic ring and their addition salts, with activity against heart failures and allergic conditions.

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N-(2-substituted alkyl)-N'-/̲imidazole-4-yl)alkyl̲7 guanidine.

The invention relates to a N-(2-substituted alkyl)-N'-/̲(imidazole-4-yl) alkyl̲7guanidine.

Impromidine, or N-/̲2-(5-methylimidazole-4-yl methylthio)ethyl̲7-N'-/̲3-(imidazole-4-yl)propyl̲7guanidine is known as a specific and the most potent histamine H_2-agonist, Dependent on the used test system it either behaves like a partial or like a complete agonist having a potency of 5-800 times that of histamine (Proc. VIIIth Internat. Symp. Med. Chem. Uppsala, pages 202-203 (1985) Eds R.Dahlbom and J.L.G. Nilsson). Because of its effect on the release of histamine from mast cells, there might be some use of impromidine in the treatment of allergic conditions. However, a major drawback for the clinical use of impromidine is its relatively high potency in stimulating the gastric acid secretion and its effect on vasoconstriction and vasodilation.

Now a series of new impromdine-related compounds was discovered, said compounds having a high histamine H_2-agonistic acitivity on the guinea-pig right atrium with a relatively low activity on the guinea-pig gastric acid secretion and a potent histamine H_1-antagonism as tested on both the guinea-pig ileum and the guinea-pig trachea.Because of this combination of histamine H_1-antagonism and H_2-agonism in one compound, these compounds are of clinical

significance for e.g. the treatment of congestive heart failures and some allergic conditions.

These new compounds are N-(2-substituted alkyl)-N'-[imidazole-4-yl)alkyl]guanidines of formula 1, wherein:

m is 1, 2 or 3;

n is 2 or 3;

X is a) S, O or CH_2, and

Y is a R substituted diphenylmethyl group or (10,11-dihydro) 5H-dibenzo-[*a*-*d*]-cycloheptene-5-yl group, or

is b) $\underset{\substack{| \\ Y_1}}{N}$, wherein

Y_1 is a R-substituted phenyl group and

Y is also a R-substituted phenyl group in that

Y and Y_1 need not be substituted simultaneously or

Y is a R-substituted benzyl group, or

is c) =CH-, and

Y is a R-substituted diphenylmethylidenyl group or (10,11-dihydro)-5H-dibenzo-[*a*,*d*]-cycloheptene-5-ylidene group,

R is H, alkyl, alkoxy, halogen and/or trihalogen methyl, with the understanding that from all appropriate phenyl rings one or more may be substituted by a R-substituted heterocyclic aromatic ring and

their acid addition salts.

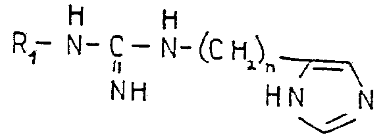
Possibly present R-substituted heterocyclic aromatic rings are for example: 2-, 3- and 4-pyridinyl, 4-imidazolyl, 4-thiazolyl, 2-guanidino-4-thiazolyl, 2- and 3-furanyl, 2-dimethylaminomethyl-5-furanyl, etc.

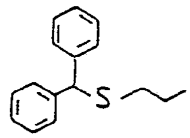
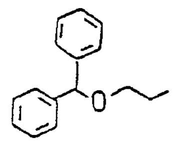
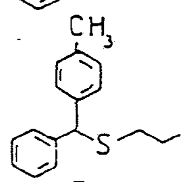
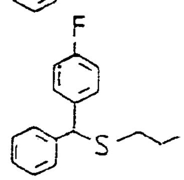
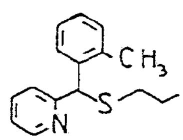
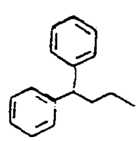
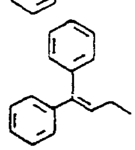
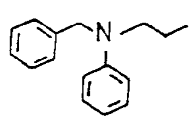
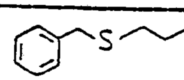
The results of pharmacological tests with said new compounds are summarized in Table A (H_1-activity) and Table B (H_2-activity). The

values for the H_1-activity given are the mean of at least two experiments in quadruplo, while the values for the H_2-activity result from at least two experiments in duplicate.

In Table A the tested compounds are defined by a formula, and the meaning of R_1 and n in the formula are stated in the table. In addition the compound have serial numbers corresponding with the serial numbers used in Table B. It is remarked that the last three compounds in the two tables do not fall within the invention, but are stated for comparison.

Table A Histamine H_1- activity



	R_1	n	Ileum (pA2 0,2)	Trachea pA2 (±0,2)
I		3	6,5	6,2
II		2	6,4	not determined
III		3	7,5	7,6
IV		3	6,4	6,5
V		2	6,6	not determined
VI		3	6,6	6,8
VII		3	6,4	6,0
VIII		2	6,2	not determined
IX		3	6,3	not determined
X		3	6,7	6,2
XI		3	7,6	7,8
XII	 [3]	3	5,5	not determined

continuation of table A

XIII	Impromidine	5,5	not determined
XIV	Diphenhydramine	8,0	not determined

Table B Histamine H_2- activity

		atrium		gastric fundus	
		α	$pD_2(\pm 0,1)$	α	$pD_2(\pm 0,2)$
I		1,0	6,8	1,0	6,1
II		0,8	4,8	0,5	4,9
III		0,9	5,5	0,4	5,8
IV		0,8	5,9	not determined	
V		0	4,0	0	4,0
VI		0,8	5,9	0,4	5,5
VII		0,8	5,9	not determined	
VIII		0,9	5,6	0	5,0
IX		1,0	7,7	not determined	
X		1,0	7,0	0,9	5,6
XI		1,0	6,4	0,7	6,5
XII		1,0	7,2	1,0	7,6
XV	Histamine	1,0	6,1	1,0	5,5
XIII	Impromidine	1,0	7,8	1,0	8,5

Discussion

H_1-activity

There is no change in H_1-activity when changing the 5-methylimidazole part of impromidine in a phenyl group (compound XII). However, introducing an extra phenyl group in compound XII results in an increase in pA_2 from 5.5 to 6.5 (Compound I) on the guinea-pig ileum. Shortening the trimethylene chain in compound I to an ethylene chain (compound II) has no effect on the H_1-activity. Analogous results have been obtained when comparing compound IV with compound V and compound VIII with compound IX.

Substituting an oxygen for the sulphur atom (compound III) turned out to be ten times as potent as the starting compound on the guinea-pig ileum and even 25 times as potent on the trachea.

Introducing a paramethyl group (compounds IV and V) or a parafluoro group (compound VI) has only little or no effect at all on the H_1-antagonism.

Also compounds VII, VIII, IX and X are almost as potent H_1-antagonists as compound I. Compound XI seems to be even a slightly more potent H_1-antagonist than the oxygen analogue compound II.

H_2-activity

Replacing the 5-methylimidazole group of impromidine by a phenyl group (compound XII) is attended with a 4-fold decrease in H_2-activity on the guinea-pig atrium and an 8-fold decrease on the gastric fundus. Introduction of an extra phenyl group in compound XII (compound I) results in a 2 à 3 fold reduction in H_2-agonism on the atrium and even 32-fold decrease in H_2-agonism on the fundus.

Shortening the trimethylene chain of compound I to an ethylene chain

(compound II) results in a marked decrease in H_2-activity, both on the atrium and on the fundus. Analogous results have been obtained with the compound IV with regard to compound V and the compound VIII with regard to compound IX.

Replacing the sulphur atom in compound I by an oxygen atom (compound III) results in a 20-fold decrease in H_2-agonism on the atrium. On the gastric fundus the change in pD_2 is less pronounced but in this test system this change in structure is attended with a remarkable decrease in intrinsic activity.

Also introduction of a para methyl group (compounds IV and V) or a para fluor group (compound VI) results in a strong decrease in H_2-activity.

Compound VII was found to be an almost as potent H_2-antagonist as the para methyl and fluoro analogues.

When the sulphur atom in compounds I and II is omitted, the diphenylpropyl analogues, compounds VIII and IX are obtained. These compounds show a remarkable high potency on the guinea-pig right atrium. Compound IX was found to be almost as potent as impromidine on the atrium.

Introduction of a double bond (compound X) results in a 4-fold decrease in H_2-activity on the atrium. The amino analogue, compound XI, proved to be about twice as potent as histamine on the atrium and to have about 4% of the activity of impromidine in this test system. On the gastric fundus this compound has about 1% of the activity of impromidine and 10 times the activity of histamine.

Conclusions

The oxygen analogue, compound III, and the amino analogue, compound XI, turned out to be the most potent H_1-antagonists of this series of impromidine analogues.

Compounds I, IX and X proved to be the most potent compounds of this series on the guinea-pig right atrium.

Because of their combination of qualities compounds I, IX, X and XI are the most preferred compounds.

The pharmacological tests were carried out as follows:

Guinea-pig trachea (H_1)

Male guinea-pigs (350-500 g) were killed by a blow on the head and the trachea removed. Single segments were cut from the trachea, loaded with 0.4 g and placed in an organ bath (35°C) containing 120 mM NaCl, 6 mM KCl, 1mM $MgSO_4$, 2.5 mM $CaCl_2$, 1mM NaH_2PO_4, 2.5 mM $NaHCO_3$ and 6 mM glucose. The organ bath was gassed with oxygen containing 5% CO_2. PD_2, intrinsic acitivity and antagonistic activity of the test compounds were determined from isotonically recorded, cumulative dose-response curves.

The H_1-specificity of the organ has been established by blocking the histamine induced contractions of the trachea with mepyramine. Moreover, both the specific histamine H_2-agonist dimaprit (up to 10^{-3} M) and the specific histamine H_2-antagonist cimetidine (up to 10^{-4} M) proved to have neither effect on the resting state of the organ nor on the histamine induced contractions.

Guinea-pig ileum (H_1)

Histamine H_1-activity at the guinea-pig ileum has been determined as described by Emmett et al. J.Med.Chem., 25, 1168-1174 (1982).

Guinea-pig right atrium H_2

Histamine H_2-activity at the guinea-pig right atrium has been determined as described by Sterk et al. Eur.J.Med. - Chim.Ther., 19, 545-550 (1984).

Guinea-pig gastric acid secretion (H_2)

Histamine H_2-activity at the acid secretion of the isolated gastric fundus of the guinea-pig has been determined as described by Impicciatore et al. Eur. J. Pharmacol., 48, 249-254 (1975).

Synthesis

The present compounds are prepared according to reaction scheme A or B. In these reaction schemes R_x corresponds with the group Y-X-(CH_2)m - of formula 1.

The primary amines used in step 1 and step 5, were prepared according to methods described in the literature or were commercially available (3.3-diphenyl propylamine).

The reaction of the primary amines with benzoylisothiocyanate to the benzoyl thiourea derivatives (step 1) proceeded with high yields (66-88%). The hydrolysis of these benzoylthioures derivatives (step 2) also proceeded with high yields (80-93%). The isothioureas resulting from the reaction of the thioureas with methyl iodide (step 3) were not isolated, but reacted directly, after evaporating the excess of methyl iodide, with 4-(3-aminopropyl)imidazole or 4-(2-aminoethyl)imidazole (step 4). The last reaction gave only poor yields (8-30%)no matter how long the reaction time (up to 140 hours refluxing in propanol-1).

The compounds with a basic group in the 'R_x part' (compounds VII and XI) were synthesized via their corresponding cyano-guanidine. The primary amines were first reacted with dimethyl-cyanoimino-dithiocarbonate (step 5). This reaction proceeded very well and resulted in high yields of the isothioureas (about 70%). These N-cyanoisothioureas were reacted with 4-(β-aminopropyl) imidazole to the cyanoguanidines (step 6). This reaction gave only very poor yields (10-20%). Also in this case no increase in yield could be observed when increasing the reaction time beyond 70 hours.

The hydrolysis of these cyanoguanidines to the end products (compounds VII and XI) gave an almost quantitative yield. These products were purified as their tripicrates in order to remove the ammoniumchloride formed in this hydrolysis.

Synthesis of the amines

2-(diphenylmethylthio)ethylamine. HCl. (A_1)

This compound is prepared according to R.G. Hiskey and M.A. Harpold Tetrahedr., 23, 3923-3929 (1967).

2-(diphenylmethoxy)ethylamine.maleic acid (A_2)

This compound is prepared according to Van der Stelt et al. Arzneimitt.Forsch. 17, 1446-1449 (1967).

General process for the synthesis of 2-/alpha-phenyl-4-methyl-benzylthio/ethylamine (A_3) and 2-/alpha-phenyl-4-fluorbenzylthio/ ethylamine.HCl (A_4)

Compounds A_3 and A_4 are prepared analogous to the method mentioned for the preparation of compound A_1.

A solution of 0.2 mole of the desired substituted benzhydrol, 0.2 mole of cysteamine and 28 ml of borontrifluoride etherate in 200 ml of acetic acid was refluxed for one hour. After cooling the solution was evaporated and the residue crystallized from 2-propanol/ether.

Results:

A_3: the free base was distilled under reduced pressure, boiling point $_{0.1}$: 115-120°C.

melting point of the dihydrogen maleate: 125-128°C.

yield: 86%

^{1}H-NMR: ($CDCl_3$, free base):

1.32 ppm, singlet, 1.8 H; 2.28 ppm, singlet, 3.0H;

2.36-2.94 ppm, multiplet, 4.0 H; 5.12 ppm, singlet, 1.0H;

6.77-7.60 ppm, multiplet, 9.3 H.

A_4: melting point 144-148°C

yield: 92%

^{1}H-NMR ($CDCl_3$, free base): 1.28 ppm, singlet, 2.0H;

2.35-2.98 ppm, multiplet, 4.0 H;

5.12 ppm, singlet, 1.0 H;

6.76-7.54 ppm, multiplet, 9.2 H.

3.3-diphenylprop-2-enylamine, HCl (A_5)

This compound can be prepared according to Jones et al. J.Med.Chem., 14, 161-164 (1971).

3.3-diphenylpropylamine (A_6)

This compound is commercially available.

N-benzyl-N-phenylethylenediamine.HCl (A_7)

This compound is prepared according to US-A- 2 505 133.

General procedure for the preparation of the benzoylthioures derivatives (B_1 - B_6)

A solution of about 20 g of the free base of the corresponding amine (A_1 - A_6) in 100 ml of $CHCl_3$ was added slowly to a solution of an equimolar amount of benzoylisothiocyanate in 100 ml of $CHCl_3$. The resultant solution was refluxed for 15 minutes and subsequently concentrated under reduced pressure to approximately 50 ml. Addition of diethyl ether caused

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crystallisation. The precipitate was filtered off, washed with ether and dried.

N-benzoyl-N'-/2-(diphenylmethylthio)ethyl/thiourea (B_1)

Yield: 88%

melting point : 101-103°C

^{1}H-NMR($CDCl_3$):2.70 ppm, triplet, J = 6.0 Hz, 2.1 H;
3.78 ppm, quartet, J = 6.0 Hz, 2.0 H;
5.26 ppm, singlet, 1.0 H;
7.04 - 7.96 ppm, multiplet, 16.0 H;
8.96 ppm, singlet (b), 0.9 H;
10.9 ppm, triplet (b), J = 5.8 Hz, 0.9 H.

N-benzoyl-N'-/2-(diphenylmethoxy)ethyl/thiourea (B_2)

Yield: 87%

melting point: 123-125°C

^{1}H-NMR ($CDCl_3$): 3.60 ppm, triplet, J = 5.5 Hz, 2.0H; 3.90 ppm, quartet, J = 5.4 Hz, 2.0 H; 5.34 ppm, singlet, 1.0 H; 7.02-7.88 ppm, multiplet, 15.0 H; 8.88 ppm, singlet (b), 0.9 H; 11.00 ppm, singlet (b), 0.9 H.

N-benzoyl-N'-2-/alpha-phenyl-4-methylbenzylthio/ethylthiourea (B_3)

Yield: 87%

oil, purified by column chromotography (silica 0.063-0.200mm, chloroform)

^{1}H-NMR ($CDCl_3$): 2.29 ppm, singlet, 3.0 H: 2.70 ppm, triplet, J = 6.0 Hz, 2.0 H; 3.77 ppm, quartet, J = 6.0 Hz, 2.0 H; 5.26 ppm, singlet, 1.0 H: 7.02-7.94 ppm, multiplet, 15.0 H; 8.94 ppm, singlet (b), 0.9 H; 10.2 ppm, triplet (b). J = 5.6 Hz, 0.9 H.

N-benzoyl-N'-/2-(alpha-phenyl-4-fluorobenzylthio)ethyl/-thiourea (B_4)

Yield: 70%

melting point: 99-102°C

^{1}H-NMR ($CDCl_3$): 2.70 ppm, triplet, J = 5.9 Hz, 1.9 H; 3.84 ppm, quartet, J = 5.9 Hz, 1.8 H; 5.23 ppm, singlet, 0.9 H; 6.74-7.93 ppm, multiplet 14.7 H; 8.97 ppm, singlet, 0.8 H; 10.88 ppm, triplet, J = 5.9 Hz, 0.9 H.

N-benzoyl-N'-(3.3-diphenylprop-2-enyl)thiourea (B_5)

Yield: 85%

melting point: 140-141°C

^{1}H-NMR($CDCl_3$): 3.62-3.85 ppm, disturbed quartet, 1.7 H; 5.59 ppm, triplet, J = 7.1 Hz, 0.9 H; 6.38-7.29 ppm, multiplet, 15.6 H; 8.31 ppm, singlet, 0.9 H; 10.08 ppm, singlet, 0.8 Hz.

N-benzoyl-N'-(3.3-diphenylpropyl)thiourea (B_6)

Yield: 66%

melting point: 116-118°C

^{1}H-NMR($CDCl_3$): 2.47 ppm, quartet, J = 7.4 Hz, 1.3 H; 3.64 ppm, quartet, J = 7.4 Hz, 1.8H; 4.02 ppm, triplet, J = 7.4 Hz, 1.0 H; 7.00-7.96 ppm, multiplet, 15.7 H; 8.91 ppm, singlet, 0.8 H; 10.68 ppm, singlet, 0.8 H.

General procedure for the preparatioj of thioureas (C_1 - C_6).

A solution of 25 g of a benzoylthiourea (B_1-B_6) in a mixture of 200 ml acetone and 200 ml methanol was added slowly to a solution of 25 g K_2CO_3 in 200 ml H_2O at 80°C. The resultant mixture was refluxed for 2 hours. After concentrating the mixture under reduced pressure the thiourea analogue (C_1-C_6) crystallized.

N-[2-(diphenylmethylthio)ethyl]thiourea (C_1)

Yield: 86%

melting point: 67-70°C

^{1}H-NMR($CDCl_3$): 2.60 ppm, triplet, J = 6.3 Hz, 2.0 H; 3.50 ppm, singlet (b), 2.0 H; 5.22 ppm, singlet, 1.0 H; 6.00 ppm, singlet, 2.OH; 6.90 ppm, triplet (b), J = 6.0 Hz, 0.9 H; 7.14-7.56 ppm, multiplet, 10.0H.

N-/2-(diphenylmethoxy)ethyl/thiourea (C_2)

Yield: 87%

melting point: 128-130°C

^{1}H-NMR ($CDCl_3$): 3.08-3.90 ppm, multiplet (b), 4.0 H; 5.36 ppm, singlet, 1.0 H; 6.00-6.70 ppm, broad signal, 2.0 H; 7.30 ppm, singlet, 11.4 H.

N-/2-(alpha-phenyl-4-methylbenzylthio)ethyl/thiourea (C_3)

Yield: 85%

melting point: 115-117°C

^{1}H-NMR (DMSO-d_6): 2.29 ppm, singlet, 3.1 H; 2.58 ppm, triplet, J = 5.4 Hz, 2.1H; 3.10-3.80 ppm, multiplet, 2.OH; 5.16 ppm, singlet, 1.0 H; 5.90 ppm, singlet, 1.8 H; 6.79 ppm, triplet, J = 7.2 Hz, 1.0 H; 7.00-7.56 ppm, multiplet, 11.0 H.

N-/2-(alpha-phenyl-4-fluorobenzylthio)ethyl/thiourea (C_4)

Yield: 80%

melting point: 101-105°C

^{1}H-NMR ($CDCl_3$): 2.25 ppm, triplet, J = 5.4 Hz, 2.0 H; 3.02-3.92 ppm, multiplet, 2.0 H; 5.22 ppm, singlet, 2.0 H: 6.11 ppm, singlet, 1.3 H; 6.76-7.53 ppm, multiplet, 10.4 H.

N-(3.3.diphenylprop-2-enyl)thiourea (C_5)

Yield: 81%

melting point: 201-203°C

^{1}H-NMR (DMSO-d_6): 3.81-4.19 ppm, multiplet, 2.1 H; 6.12 ppm, triplet, J = 6.3 Hz, 1.0 H; 6.73-7.58 ppm, multiplet, 10.9 H; 8.31 ppm, singlet, 2.1 H.

N-(3.3-diphenylpropyl)thiourea (C_6)

Yield: 93%

melting point: 197-199°C

^{1}H-NMR ($CDCl_3$): 2.32 ppm, quartet, J = 7.2 Hz, 2.0 H; 3.13-3.60 ppm, multiplet, 2.0 H; 4.00 ppm, triplet, J = 7.2 Hz, 1.0H; 6.40 ppm, singlet, 2.0 H; 6.94-7.60 ppm, multiplet, 11.4 H.

N-[2-(N'-benzyl-N'-phenylamino)ethyl]-N"-cyano-S-methylisothiourea (C_7)

A solution of 15 g of N-benzyl-N-phenylethylenediamine in 100 ml of ether was added slowly to a stirred solution of N-cyanodimethyliminodithiocarbonate in 100 ml of ether. The resulting solution was stirred for 2 hours, after which the precipitate was filtered off, washed with either and dried.

Yield: 70 %

melting point: 148-152°C

^{1}H-NMR ($CDCl_3$): 2.33 ppm, singlet, 2.6 H; 3.30-3.76 ppm, multiplet, 4.1 H; 4.55 ppm, singlet, 1.8 H; 6.59-6.95 ppm, multiplet, 3.4 H; 7.10-7.50 ppm, multiplet, 7.3H.

N-cyano-S-methyl-N'-(2-[2-methyl-alpha-(2-pyridyl)benzylthio]ethyl) isothiourea (C_8)

A solution of 20 mg of 2 methylphenyl-2-pyridylmethanol and 11.4 g of cysteamine in 300 ml 48% HBr was refluxed for 5 hours and subsequently evaporated. The residue was dissolved in H_2O, brought at pH 11 with KOH, after which the aqueous phase was extracted

with $CHCl_3$. The $CHCl_3$-layer was dried over $MgSO_4$ and evaporated. The residue was dissolved in ether and added slowly to a solution of 15 g of N-cyanodimethyliminodithiocarbonate. After stirring for 3 hours, the precipitate was filtered off, washed with ether and dried.

Yield: 60%

melting point: 96-99°C.

^{1}H-NMR ($CDCl_3$): 2.34 ppm, singlet, 2.9 H; (2.56 ppm, singlet; 2.71 ppm, triplet, J = 6.3 Hz) together: 5.1 H; 3.51 ppm, quartet, J = 6.3 Hz, 2.0 H; 5.47 ppm, singlet, 1.0 H; 7.01-7.75 ppm, multiplet, 8.2 H; 8.47-8.64 ppm, multiplet, 0.9 H.

General procedure for the synthesis of the guanidines of examples I-VI and VIII-X.

A solution of 10 g of a thiourea (C_1-C_6) and 1.2 equivalents of methyl iodide in 200 ml of methanol was stirred for 18 hours at room temperature. After evaporating the solvent, a solution of 2.5 g of 4-(3-aminopropyl)imidazole or 4-(2-aminoethyl)imidazole in 200 ml of ethanol was added to the residue. The resultant mixture was refluxed for 70 hours and the product was purified by columnchromatography (silica gel 0.063-0.200 mm).

General procedure for the synthesis of the guanidine derivatives of examples VII and XI.

A solution of 12 g of the appropriate S-methylisothiourea derivative (C_7 or C_8) and 2.5 g of 4-(3-aminopropyl)imidazole in 300 ml ethanol was refluxed for 70 hours. After evaporating the solvent the residue was applied to a silica column and eluted with 50% mixture of ethanol and chloroform. The fractions containing pure nitrile, were collected, the solvent was evaporated and the residue dissolved in 2 N HCl. After refluxing for 3 hours the reaction mixture was evaporated and the residue

dissolved in methanol and added to a solution of picric acid in methanol. The precipitated oil was washed thoroughly with methanol and dried in vacuo on which the oil solidified.

Example I

N-/2-(diphenylmethylthio)ethyl/-N'-/3-(imidazole-4-yl)propyl/guanidine dihydrogenmaleate

Elution with ethanol. The compound was crystallized in the presence of an excess of maleic acid from ethanol/ether.

Yield: 12%

melting point: 119-123°C

^{1}H-NMR (DMSO-d_6): 1.82 ppm, quintet, J = 7.2 Hz, 2.0 H; 2.38-2.82 ppm, multiplet, (+DMSO-d_5), 6.0 H; 3.01-3.50 ppm, multiplet, 4.0 H: 5.42 ppm, singlet, 1.0 H; 6.06 ppm, singlet, 4.0 H; 7.08-7.72 ppm, multiplet, 15.5 H; 8.85 ppm, doublet, J = 0.8 Hz, 0.9 H.

Example II

N-/2-(diphenylmethylthio)ethyl/-N'-/2-imidazole-4-yl)ethyl guanidine.dihydrogenmaleate

Elution with a 50% mixture of ethyl acetate and ethanol. The compound was crystallized in the presence of an excess of maleic acid from ethanol/ether.

Yield: 22%

melting point: 152-155°C.

^{1}H-NMR (DMSO-d_6): 2.52 ppm, triplet. J = 5.9 Hz, (+DMSO-d_5), 3.0 H: 3.86 ppm, triplet, J = 5.9 Hz, 2.0 H; 3.10-3.64 ppm, multiplet, 4.0 H; 5.41 ppm, singlet, 1.0 H; 6.09 ppm, singlet, 4.0 H; 7.16-7.72 ppm, multiplet, 15.4 H; 8.74 ppm, singlet 1.0 H.

Example III

N-/2-(diphenylmethoxy)ethyl/-N'-/3-(imidazole-4-yl)propyl/ guanidine. 3/2 dihydrogenmaleate

Elution with propanol-2 and crystallized in the presence of an excess of maleic acid from methanol/ether.

Yield: 8%

melting point: 132-135°C

^{1}H-NMR (DMSO-d_6): 1.74 ppm, quintet, J = 7.2 Hz, 2.0 H; 2.60 ppm, triplet (+DMSO-d_5), J = 7.2 Hz, 2.1 H; 3.00-3.60 ppm, multiplet (+H_2O) 6.0 H; 5.46 ppm, singlet, 1.0 H; 6.02 ppm, singlet, 3.0 H; 7.06-7.62 ppm, multiplet, 14.0 H; 8.76 ppm, singlet, 0.9 H.

Example IV

N-/3-(imidazole-4-yl)propyl/-N'-2-/α-phenyl-4-methylbenzylthio/ ethyl guanidine dipicrate

Elution with a 50% mixture of ethyl acetate and ethanol. The product was crystallized in the presence of an excess of picric acid from methanol/H_2O.

Yield: 18%

melting point: 76-78°C

^{1}H-NMR (DMSO-d_6): 1.78 ppm, quintet, 2.0 H; 2.22 ppm, singlet, 3.0H; 2.31-2.74 ppm, multiplet, 11.0H(+DMSO-d_5); 3.00-3.73 ppm, multiplet, 12.0H (H_2O); 5.28 ppm, singlet, 1.0H; 6.90-7.53 ppm, multiplet, 11.4H; 8.52 ppm, singlet, 4.0H; 8.92 ppm, singlet, 1.2H; 14.00 ppm, singlet, 2.0 H.

Example V

4-/2-(imidazole-4-yl)ethyl/-N'-2-/α-phenyl-4-methylbenzylthio/ethyl guanidine. dihydrogen maleate

Elution with a 50% mixture of ethylacetate and propanol-2. The product was crystallized in the presence of an excess of maleic acid from propanol-2/ethylacetate.

Yield: 32%

melting point: 119-121°C.

^{1}H-NMR (DMSO-d_6) : 2.24 ppm, singlet, 2.8H; 2.32-2.65 ppm , multiplet, 9.1 H (+DMSO-d_5) ; 2.80 ppm, triplet, J = 6.3 Hz, 2.0H; 3.14-3.62 ppm, multiplet, 3.8 H; 5.33 ppm, singlet, 1.0H; 6.05 ppm, singlet, 4.0H; 7.00-7.62 ppm, multiplet, 14.8 H; 8.63 ppm, singlet, 1 OH.

Example VI

N-/2-(α-phenyl-4-fluorobenzylthio)ethyl/-N'-/3-(imidazole-4-yl) propyl/guanidine. dihydrogenoxalate

Elution with a 50% mixture of ethylacetate and propanol-2. The compound was crystallized in the presence of an excess of oxalic acid from methanol/ethylacetate.

Yield: 15%

melting point: 83-85°C

^{1}H-NMR: (dipicrate; DMSO-d_6) 1.70-1.96 ppm, quintet, J = 6.9 Hz, 1.9H; 2.34-2.90 ppm, multiplet, (+DMSO-d_5), 5.1H; 3.00-3.53 ppm, multiplet, 4.0H; 5.43 ppm, singlet, 1.0H: 7.00-7.87 ppm, multiplet, 15.4 H; 8.60 ppm, singlet, 3.9 H: 9.03 ppm, doublet, J = 0.8 Hz, 0.8 H: 14.05 ppm. singlet (b) 2.1 H.

Example VII

N-/3-(imidazole-4-yl)propyl/-N'-(2-/2-methyl-alpha-(2-pyridyl) benzylthio/ethyl)guanidine. tripicrate

Yield: 5%

melting point: 98-102°C

^{1}H-NMR (DMSO-d_6); 1.82 ppm, quintet, J = 7.0 Hz, 2.0H; 2.38 ppm, singlet, 3.0H; 2.45-2.83 ppm, multiplet, (+DMSO-d_5), 7.8 H; 3.02-3.60 ppm, multiplet, 4.0H; 5.68 ppm, singlet, 1.0H; 7.08-8.83 ppm, multiplet, 19.0H; 9.03 ppm, singlet, 1.0H; 14.02 ppm, singlet (b), 2.0H.

Example VIII

N-(3.3-diphenylpropyl)-N'-/2-(imidazole-4-yl)ethyl/ guanidine. dihydrogen maleate.

Elution with a 50% mixture of ethylacetate and ethanol. The product was crystallized in the presence of an excess of maleic acid from propanol-2/ethylacetate.

Yield: 32%

melting point: 115-118°C

^{1}H-NMR (D_2O): 2.33 ppm, quartet, J = 7.3 Hz, 2.0H; 2.94 ppm, triplet, J = 7.1Hz, 2.0H; 3.16 ppm, triplet, J = 7.1 Hz, 2.0H; 3.41 ppm, triplet, J = 7.1 Hz, 2.0H; 4.03 ppm, triplet, J = 7.3 Hz, 1.0H; 6.34 ppm, singlet, 4.3H; 7.15-7.44 ppm, multiplet, 10.5H; 8.56 ppm, doublet, J = 1.2 Hz, 0.8 H.

Example IX

N-(3.3-diphenylpropyl)-N'-/3-(imidazole-4-yl)propyl/guanidine. dipicrate

Elution with a 50% mixture of ethylacetate and ethanol. The product was crystallized in the presence of an excess of picric acid from propanol-2/ether.

Yield: 12%

melting point: 73-77°C.

^{1}H-NMR (DMSO-d_6): 1.78 ppm, quintet, J = 7.5 Hz, 2.0H; (2.32 ppm, triplet, J = 7.5 Hz; 2.68 ppm, triplet,

J = 7.5 Hz) together (+DMSO-d_5) 8.3 H; 2.87-3.30 ppm, multiplet, 4.0H; 4.00 ppm, triplet, J = 7.5H_z, 1.0H; (7.28 ppm, singlet: 7.43 ppm, singlet) together 16.2H; 8.60 ppm, singlet, 4.0H; 9.00 ppm, doublet, J = 0.8 Hz, 1.0H; 14.13 ppm, singlet (b). 2.0H.

Example X

N(3.3-diphenylprop-2-enyl)-N'-/3-imidazole-4-yl)propyl/ guanidine. H1

Crystallized from ethanol/diethylether.

Yield: 10%

melting point: 73-76°C.

^{1}H-NMR (DMSO-d_5): 1.80 ppm, quintet, J = 7.0 Hz, 2.0H; 2.39-2.80 ppm, multiplet, (+DMSO-d_5) 4.1H; 2.94-3.37 ppm, multiplet, 2.0H; 2.84 ppm, triplet, J = 7.0 Jz, 2.0H; 6.13 ppm, triplet, J = 7.0 Hz, 1.0H; 7.00-8.20 ppm. multiplet, 16.5 H: 8.35 ppm, singlet, 1.0H.

Example XI

N-/2-(N'-benzyl-N'-phenylamino)ethyl/-N"-/3-(imidazole-4-yl) propyl/guanidine, tripicrate

Yield: 6%

^{1}H-NMR (DMSO-d_6): 1.80 ppm, quintet, J = 7.0 Hz, 2.0H; 2.42-2.85 ppm, multiplet, (+DMSO-d_5) 4.4 H+ 2.97-377 ppm, multiplet (+H_2O) 6.6 H; 4.62 ppm, singlet, 2.0H; 6.41-7.74 ppm, multiplet, 17.0H; 8.64 ppm, singlet, 6.0H; 9.03 ppm, singlet, 1.0H; 14.20 ppm, singlet (b), 2.0H.

CLAIMS:

1. N-(2-substituted alkyl)-N'-/(imidazole-4-yl) alkyl)/guandine characterized in that it has the formula 1, wherein

m is 1, 2 or 3;

n is 2 or 3

X is a) S.O or CH_2, and

Y is a R substituted diphenylmethyl group or (10,11-dihydro) 5H-dibenzo-/a-d/-cycloheptene-5-yl group, or

is b) $\underset{\underset{Y_1}{|}}{N}$, wherein

Y_1 is a R-substituted phenyl group and

Y is also a R-substituted phenyl group in that

Y and Y_1 need not be substituted simultaneously or

Y is a R-substituted benzyl group, or

is c) =CH-, and

Y is a R-substituted diphenylmethylidenyl group or (10,11-dihydro)-5H-dibenzo-/a,d/-cycloheptene-5-ylidene group,

R is H, alkyl, alkoxy, halogen and/or trihalogen methyl, with the understanding that from all the appropriate phenyl rings one or more may be substituted by a R-substituted heterocyclic aromatic ring and their acid addition salts.

2. Compound according to claim 1, characterized in that n = 3.

3. Compound according to claim 1, characterized in that X is a sulphur atom.

4. Compound according to claim 1, characterized in that m is 2.

5. Compound according to claim 3, characterized in that X is =CH-.

6. Compound according to claim 1, characterized in that

X is $\underset{\underset{Y_1}{|}}{N}$

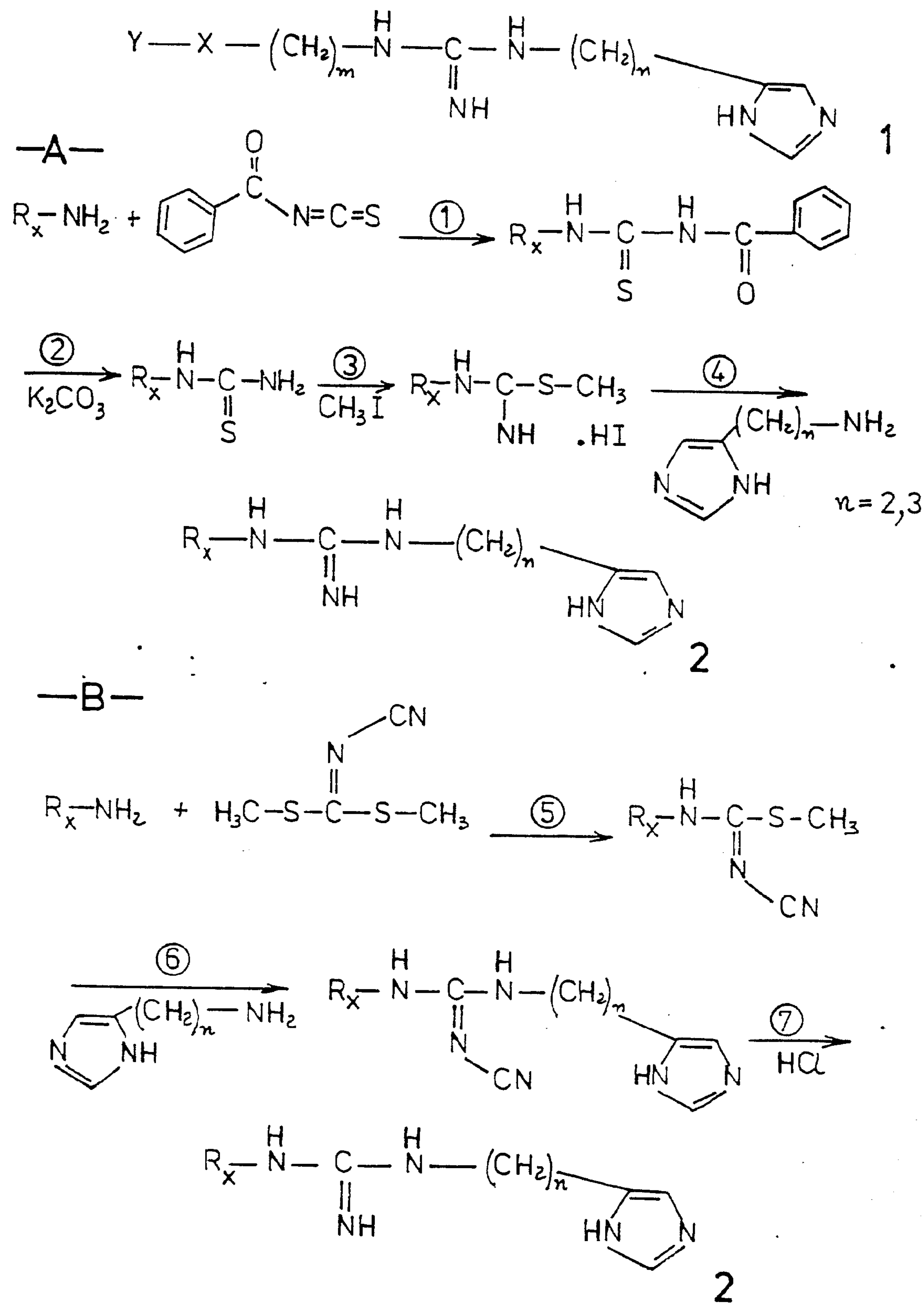
7. Compound according to claim 1, characterized in that R is hydrogen.

8. Process for the preparation of a compound according to claim 1, characterized in that a primary amine of the formula R_xNH_2, wherein R_x corresponds with the appropriate group $Y\text{-}X\text{-}(CH_2)_m$ of formula 1, is reacted with benzoylisothiocyanate to a benzoylthiourea derivative, followed by hydrolysis of this derivative to the corresponding thiourea, converting this thiourea with methyliodide into an isothiouerea and producing the desired compound by reaction with aminopropylimidazole or aminoethylimidazole, and possibly converting said compound into an acid addition salt or producing the free compound from such an obtained salt.

9. Process for the preparation of a compound according to claim 1, characterized in that a compound having a basic group in the substituent to the N'-alkyl group is prepared, by reacting a primary amine of the formula R_xNH_2, wherein R_x corresponds with the appropriate group $Y\text{-}X\text{-}(CH_2)_m$ of formula 1, with dimethylcyano iminodithiocarbamate to a N-cyano isothiourea, followed by reaction of this N-cyano isothiourea with aminopropylimidazole to the cyano guanidine and producing by hydrolysis the desired compound and possibly converting said compound into an acid addition salt, or producing the free compound from such an obtained salt.

10. Pharmaceutical composition for the treatment of congestive heart failures and some allergic conditions, characterized in that the composition comprises at least one compound of the formula 1, as defined in claims 1-7 or an acid addition salt thereof, as an active substance.

11. Process for preparing a pharmaceutical composition according to claim 10, characterized in that therefore a compound according to one of claims 1-7 is used.


1
—A—
①
②
K2CO3
③
CH3I
.HI
④
n = 2,3
2
—B—
⑤
⑥
⑦
HCl
2

INTERNATIONAL SEARCH REPORT

International Application No PCT/NL 87/00013

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: C 07 D 233/64; C 07 D 401/12; A 61 K 31/415; A 61 K 31/33

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	C 07 D 233/00 C 07 D 401/00 A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	US, A, 4013659 (DURANT et al.) 22 March 1977 --	
A	US, A, 4166860 (DOUGLAS et al.) 4 September 1979 --------	

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
7th September 1987	- 6 OCT 1987
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	L. ROSSI

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/NL 87/00013 (SA 17715)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 16/09/87

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A- 4013659	22/03/77	US-A-	4152443	01/05/79
		NL-A-	7408942	15/01/75
		BE-A-	816850	27/12/74
		DE-A-	2433625	30/01/75
		LU-A-	70507	28/11/74
		FR-A,B	2274298	09/01/76
		AU-A-	6984574	11/12/75
		GB-A-	1431589	07/04/76
		US-A-	4025527	24/05/77
		CH-A-	601252	30/06/78
		US-A-	4112104	05/09/78
		AT-B-	346855	27/11/78
		CA-A-	1049524	27/02/79
		JP-A-	50032174	28/03/75
		US-A-	4215125	29/07/80
		OA-A-	4814	31/10/80
		US-A-	4271169	02/06/81
		SE-A-	7409188	14/01/75
		US-A-	4388319	14/06/83
		SE-B-	416202	08/12/80
		US-A-	4499101	12/02/85
		GB-A-	1531237	08/11/78
US-A- 4166860	04/09/79	None		